FDA Alert for Healthcare Professionals

Natalizumab (marketed as Tysabri)

FDA ALERT [02/28/2005]: Biogen-IDEC has suspended marketing of Tysabri and all further dosing of patients in on-going clinical trials. This decision was made after confirmation of one fatal case and one additional case of progressive multifocal leukoencephalopathy (PML) in patients receiving Tysabri for multiple sclerosis (MS). Both patients were enrolled in a long-term clinical trial and had been taking Tysabri for more than two years. There have been no previous cases of PML reported in patients taking Tysabri. Studies are underway by Biogen-IDEC to determine as rapidly as possible whether there is evidence of PML from patients that have received Tysabri in clinical trials.

Although these two confirmed cases of PML do not necessarily represent a causal association between use of this agent and PML, additional information needs to be obtained to fully understand the connection between Tysabri use and PML.

This information reflects FDA's preliminary analysis of data concerning this drug. FDA is considering, but has not reached a final conclusion about, this information. FDA intends to update this sheet when additional information or analyses become available.

To report any unexpected adverse or serious events associated with the use of Tysabri, please contact the FDA MedWatch program at 1-800-FDA-1088 or http://www.fda.gov/medwatch/report/hcp.htm

Recommendations

- Biogen-IDEC is voluntarily suspending marketing of Tysabri.
- Biogen-IDEC is suspending dosing of Tysabri in clinical trials and is notifying patients and investigators of the possible association between Tysabri and PML.
- Patients being treated with Tysabri should contact their doctor to discuss appropriate alternative treatments.

Data Summary

At the time of approval, approximately 1,100 patients with MS had received Tysabri for a period of one year or more. No cases of PML were observed during the clinical trials performed prior to approval of Tysabri.

On February 18, FDA received a report from Biogen-IDEC, the manufacturer of Tysabri, of one confirmed, fatal case and one possible case of progressive multifocal leukoencephalopathy

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(PML) in patients receiving Tysabri for multiple sclerosis (MS). On March 3, 2005, Biogen contacted the FDA to report that the second case has been confirmed as a diagnosis of PML. Both patients were enrolled in a long-term clinical trial and had been taking Tysabri for more than two years. There have been no other cases of PML reported in patients starting Tysabri, since it was approved.

PML is a serious, progressive neurologic disorder caused by infection of the central nervous system by JC virus, a member of the papovavirus family. JC virus is carried in a latent form by 70-75% of the general population but generally does not cause symptoms. However, in severely immunosuppressed individuals, such as patients with advanced HIV infection, transplant recipients receiving immunosuppressive medications, and patients with hematologic malignancies, JC virus may become reactivated and cause PML. Although there was a slight increase in serious infections (such as pneumonia) in patients receiving Tysabri compared to those receiving placebo in controlled clinical trials (2.1% vs. 1.3%), there were no cases of opportunistic infections characteristic of immunosuppression in Tysabri-treated patients. The presentation of PML may overlap with that of MS. Distinction between the two frequently requires pathologic examination of a brain biopsy. PML frequently results in irreversible neurologic deterioration and death. There is no known effective treatment for PML itself, although immune reconstitution may allow the progress of the disease to be slowed or arrested.

Although these two confirmed cases of PML do not necessarily represent a causal association between use of this agent and PML, and additional information needs to be obtained to fully understand the connection between Tysabri use and PML, the FDA is extremely concerned about this event, for the following reasons:

- the rarity of this disorder in the general population
- the existence of a possible second case of PML in a patient receiving Tysabri and Avonex
- the immunosuppressive properties of Tysabri or Tysabri in conjunction with Avonex
- the high prevalence of JC virus, the causative agent of PML, in the general population
- the lack of available methods to identify MS patients at increased risk for development of PML
- the lack of effective therapy for PML
- the life-threatening nature of this adverse event
- the need for chronic administration of Tysabri to achieve any clinical benefit

Studies are underway by Biogen-IDEC to determine as rapidly as possible whether there is evidence of PML for patients that have received Tysabri in clinical trials.